Remarks

Claims 127-132 are pending in this application. Claims 19 and 23 are canceled in this paper without prejudice to Applicants' right to pursue the subject matter recited by them in one or more divisional, continuation or continuation-in-part applications. Claim 128 is amended to correct a typographical error. No new matter has been introduced.

A. Claim Objections are Obviated

On page 3 of the Office Action, claims 128, 130 and 132 are objected to due to a typographical error in claim 128. The error is corrected by the amendments to the claims introduced in this paper, and thus, Applicants respectfully request that the these objections be withdrawn.

B. The Rejection Under 35 U.S.C. § 102 Should Be Withdrawn

On pages 3-4 of the Office Action, claims 127-130 are rejected as allegedly anticipated by U.S. Patent No. 6,391,875[1] to Morgan *et al.* ("the '875 patent"). In particular, it is alleged that the claims are anticipated because the '875 patent discloses methods of treating certain affective disorders using (S,S)-hydroxybupropion. Office Action, page 4. Applicants respectfully traverse this rejection.

To anticipate, a prior art reference must disclose each and every limitation of a claim. *See, e.g., Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). Claim 127 recites, in part, the administration of a bupropion metabolite adjunctively with a pharmacologically active second agent, which is not disclosed by the '875 patent. Since the '875 patent fails to disclose each and every limitation of claim 127, Applicants respectfully point out that the pending claims are not anticipated by the '875 patent and request that the rejection be withdrawn.

[1] Equivalent to U.S. Patent No. 6,274,579 and U.S. Publication No. 2003/0064988, as the Examiner points out in the Office Action.

C. The Rejection Under 35 U.S.C. § 103(a) Should Be Withdrawn

On pages 4-5 of the Office Action, claims 131-132 are rejected as allegedly obvious over the '875 patent alone or in view of U.S. Patent No. 6,677,378 to Howard *et al.* ("the '378 patent"). In particular, it is alleged that because the '875 patent discloses the use of (S,S)-hydroxybupropion for the treatment of certain affective disorders, "it would have been obvious ... to combine secondary active agent to improve the therapeutic efficacy because the combination drug therapy is known as standard drug regimen for the treatment of psychotic conditions or other affective conditions." Office Action, page 5. To support this proposition, the Examiner provides the abstract of Post *et al.*, *Depression and Anxiety*, 5(4): 175-189 (1997) ("Post"), a copy of the full article is supplemented in this paper by Applicants for the Examiner's review. Applicants respectfully traverse this rejection.

Under current law, a prior art reference or references cannot render a claim obvious unless the PTO provides evidence that the reference or references meet a three-part test for *prima facie* obvious. To begin with, the prior art reference or references must provide "motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant." *See In re Kotzab*, 217 F.3d 1365, 1370, 55 U.S.P.Q.2d 1313, 1316 (Fed. Cir. 2000); *Princeton Biochemicals, Inc. v. Beckman Coulter, Inc.*, 2005 WL 1355127, at *4, 75 U.S.P.Q.2d 1051, 1054 (Fed. Cir. 2005). Where one reference is relied upon by the PTO, there must be a suggestion or motivation to modify the teachings of that reference. *See In re Kotzab*, 217 F.3d at 1370, 55 U.S.P.Q.2d at 1316-17. Where an obviousness determination relies on the combination of two or more references, there must be some suggestion or motivation to combine the references. *See WMS Gaming Inc. v. International Game Technology*, 184 F.3d 1339, 1355, 51 U.S.P.Q.2d 1385, 1397 (Fed. Cir. 1999); *Princeton Biochemicals, Inc.*, 2005 WL 1355127, at *4, 75 U.S.P.Q.2d at 1054; *Teleflex, Inc. v. Ficosa North America Corp.*, 299 F.3d 1313, 1334, 63 U.S.P.Q.2d 1374, 1387 (Fed. Cir. 2002). Second, the prior art references cited by the PTO must suggest to one of ordinary skill in the art that the invention would have a reasonable expectation of success. *See In re Dow Chemical*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988); *Boehringer Ingelheim Vetmedica, Inc.*, 320 F.3d 1339, 1354, 65 U.S.P.Q.2d 1961, 1971 (Fed. Cir. 2003); *Noelle v. Lederman*, 355 F.3d 1343, 1352, 69 U.S.P.Q.2d 1508, 1516 (Fed. Cir. 2004). Further, "[b]oth the suggestion and the reasonable expectation of success

'must be founded in the prior art, not in the applicant's disclosure.'" *Noelle*, 355 F.3d at 1352, 69 U.S.P.Q.2d at 1515-16 (quoting *In re Vaeck* , 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991)). Finally, the PTO must show that the prior art references, either alone or in combination, teach or suggest each and every limitation of the rejected claims. *See Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461, 1473, 43 U.S.P.Q.2d 1481, 1490 (Fed. Cir. 1997); *Litton Systems, Inc. v. Honeywell, Inc.*, 87 F.3d 1559, 1569, 39 U.S.P.Q.2d 1321, 1327 (Fed. Cir. 1996). These criteria must be satisfied with factual and objective evidence found in the prior art; an examiner's conclusory statements cannot form a basis for a *prima facie* case of obviousness. *See In re Sang-Su Lee*, 277 F.3d 1338, 1343-44 (Fed. Cir. 2002). Applicant respectfully submits that no factual and objective evidence to establish a *prima facie* case of obviousness is provided in the Office Action.

Applicants respectfully submit that a motivation or suggestion to modify the '875 patent or combine it with the '378 patent[2] did not exist prior to this invention. For example, while disclosing certain uses of (S,S)-hydroxybupropion, the '875 patent is completely silent regarding combining it with any other active agent(s), much less SSRI, 5-HT_3 inhibitor or nicotine, as claims 131-132 recite. In addition, there is no disclosure whatsoever in the '875 patent regarding the desirability of combining (S,S)-hydroxybupropion with any active agent.

The '378 patent does not cure this deficiency. The Examiner refers to the '378 patent to support the proposition that "combination drug therapy is routinely practiced in the treatment of affective disorders." Office Action, page 5. However, Applicants respectfully point out that whether "combination drug therapy is routinely practiced" is completely irrelevant to the patentability of the pending claims. This is because the prior art cited by the Examiner must satisfy the legal requirements discussed above in order to establish a *prima facie* case of obviousness. By disclosing a genus of compounds completely different from the compounds recited by the pending claims, and thus, by providing no specific suggestion or motivation to arrive at the claimed invention, the '378 patent adds nothing to the substance of the rejection.

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[2] It is unclear whether the '378 patent is cited as part of the rejection, or merely as an evidentiary reference.

Finally, the Examiner cites Post to support the assertion that it would have been obvious to combine "secondary active agent to improve the therapeutic efficacy because the combination drug therapy is known as standard drug regimen for the treatment of psychiatric conditions." Office Action, page 5. However, Applicants respectfully point out that Post itself does not support such a proposition.

While Post discloses, referring to combination therapies for bipolar depression, that there are "a panoply of treatment options now exist," Post clearly states that these potential therapies' "relative efficacy in different illness subtypes and stages remains to be better delineated, as do their optimal sequencing and use in combination in individual patients." Post, page 184, under "Summary and Conclusion." Yet, there is no disclosure or suggestion in Post regarding the desirability of the claimed combination of a bupropion metabolite and SSRI, 5-HT_3 inhibitor or nicotine. Since none the '857 patent, the '378 patent, and Post provide any motivation or suggestion to arrive at the claimed invention, Applicants respectfully submit that the rejection should be withdrawn for this reason alone.

Furthermore, quite to the contrary to what the Examiner appears to indicate, Post actually suggests the non-obviousness of specific combination therapies that may be used to treat affective disorders.[3] In this regard, Post states that when using combination therapies, "one has to be particularly careful about drug interactions and their potential for toxicity as well as therapeutic effects." *Id.* In addition, Post also teaches that "one should be aware of potential pharmacokinetic interactions" when using a combination therapy. *Id.* As can be seen from these statements, Post clearly teaches that no generalization can be made regarding any specific combination therapies for affective disorders. Post also evidences that the Examiner's statement regarding the obviousness of the combinations recited by claims 131-132 is based on an oversimplification of drug discovery process.

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[3] To the extent that the Examiner may be referring to the portion of Post that states that "initial use of several mood stabilizer drugs in combination may have a preferable long-term outcome in some rapid cycling patients" for the required motivation or suggestion, Applicants point out that this disclosure in Post is nothing more than an invitation to experiment because Post teaches that each specific combination must be carefully examined, as discussed below. As well-settled, an invitation to experiment is not a proper basis for a rejection under 35 U.S.C. § 103. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1380 (Fed. Cir. 1986).

Along the same line, there would have been no reasonable expectation of successfully making and using the claimed combinations. As discussed above, Post teaches that various factors must be given careful considerations when combination therapies are attempted. Therefore, those of ordinary skill in the art would have had no expectation, much less a reasonable expectation, of successfully making and using any combination of agents, much less the combinations recited by the claims. [4]

Finally, For these additional reasons, Applicants respectfully request that the rejection under 35 U.S.C. § 103 be withdrawn.

D. The Double Patenting Rejection Should Be Withdrawn

On pages 5-6 of the Office Action, the claims are provisionally rejected under judicially created non-statutory double patenting as allegedly unpatentable over the claims in the co-pending Application No. 09/987,930 ("the '930 application"). However, Applicants respectfully point out that the claims in these two cases are directed to different subject matter. While claims pending in this application are directed to uses of bupropion metabolites in combination with a second active agent, the claims pending in the '930 application are directed, in part, to uses of bupropion metabolites without combining them with any other active agents. As such, Applicants respectfully submit that the claims in the two cases are not obvious over one another, and thus request that the rejection be withdrawn.

Conclusion

Applicants respectfully submit that all of the pending claims are allowable, and request that rejections directed to the claims be withdrawn.

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[4] The Examiner also alleges that those of ordinary skill in the art "would have been motivated, with reasonable expectation of success, to apply combination drug therapy with SSRI, 5HT or nicotine which utilizes different underlying mechanisms where each drug's optimal dose can be lowered along with reduced side effects." Office Action, page 5. Not only is this allegation supported by no evidence or reasoning, this allegation contradicts what is disclosed in Post.

No fee is believed due for this submission. Should any additional fees be due for this submission or to avoid abandonment of the application, please charge such fees to Jones Day Deposit Account No. 503013.

Respectfully submitted,

Date January 18, 2006

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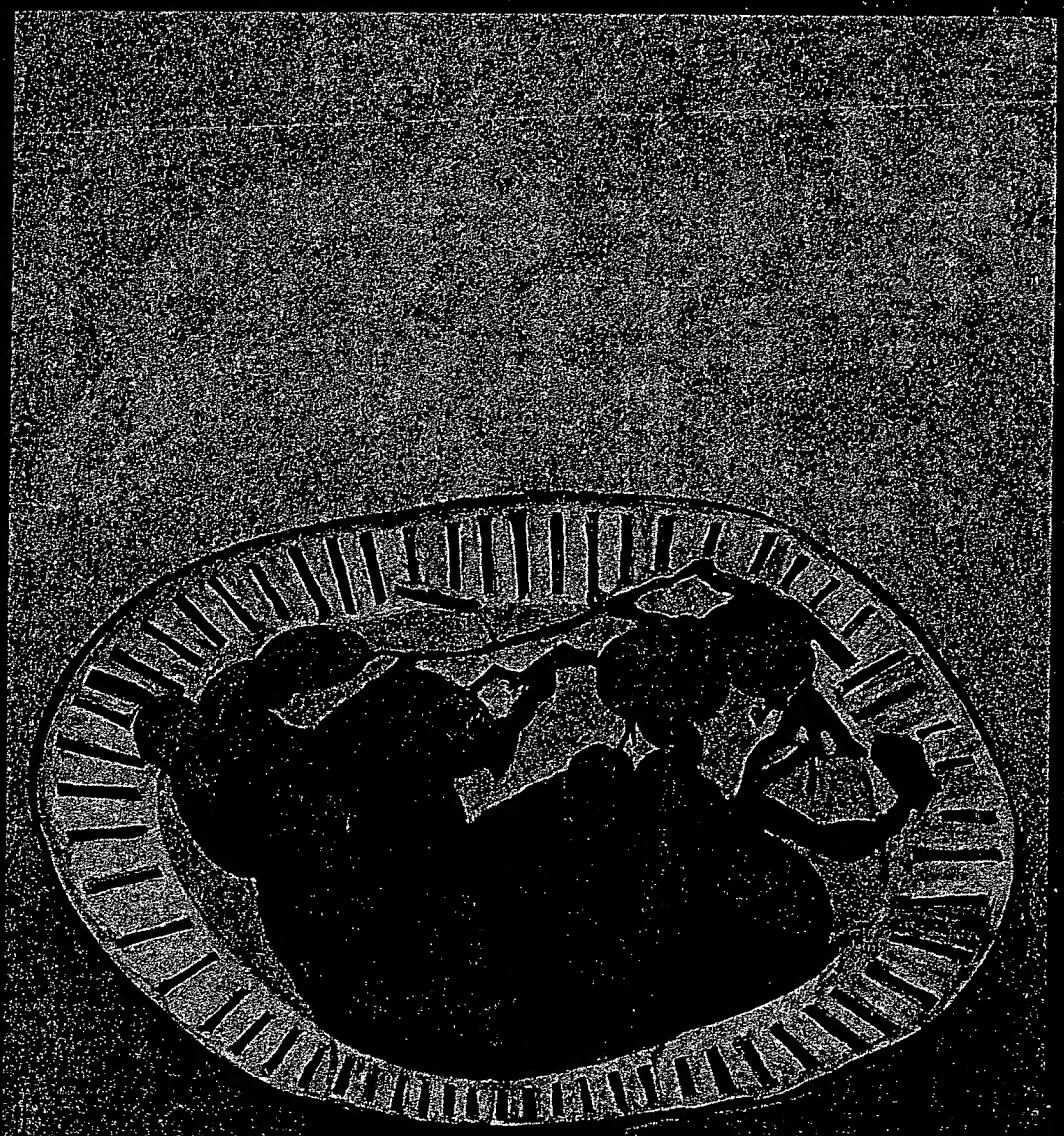
DEPRESSION AND ANXIETY



WILEY-LISS

VOLUME 5 • NUMBER 4, 199
ISSN 1091-426

DEPRESSION AND ANXIETY 5:175–189 (1997)

ALTERNATIVE APPROACHES TO REFRACTORY DEPRESSION IN BIPOLAR ILLNESS†

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Key words: *bipolar illness; refractory depression; antidepressants*

INTRODUCTION

As in other aspects of bipolar illness, variability of presentation in refractory depression is the rule. There are a variety of subtypes of refractory depression: chronic, sustained depression; episodic depression breaking through mood-stabilizing treatment; and rapid recurrences of depressive breakthroughs in the context of rapid cycling, ultra-rapid cycling, or ultra-ultra-rapid (ultradian) cycling patterns (George et al., 1997; Kramlinger and Post, 1996).

Another distinction that may ultimately have therapeutic implications is between patients who are refractory to long-term antidepressant prophylaxis from the outset, as opposed to those patients who show initially good antidepressant responsiveness but then progressively lose efficacy consistent with a pattern of tolerance (Post et al., 1990, 1996; Weiss et al., 1995). This pattern requires distinction from the phenomenon of lithium discontinuation-induced refractoriness (Post et al., 1992a, 1993). In this latter instance, patients who have had successful long-term prophylaxis with lithium discontinue treatment, experience a relapse, and then fail to re-respond to previously effective treatment. Refractoriness in this context can be extremely difficult to overcome, with patients showing not only poor response to lithium, but nonresponse to a variety of other treatment approaches as well.

The main focus of this article will be on episodic depressive breakthroughs in bipolar patients, as this appears to be the greatest problem presented. In some patients in whom refractory depression occurs persistently, the treatment algorithms more closely mirror those used in refractory unipolar patients, with complex antidepressant regimens used adjunctively with mood stabilizers.

Since this is an article on *refractory* depression in bipolar illness, we will start from the assumption that patients have already had lithium in their regimen and it was either inadequate or intolerable at sufficient doses to produce adequate antidepressant prophylaxis. It is clear that the problem of inadequate antidepressant response to lithium is not uncommon. Despite lithium's known efficacy in the prevention of recurrent unipolar depression, its adjunctive efficacy with antidepressants in unipolar depression, and its long-term prophylactic efficacy in bipolar depression, there is increasing recognition of lithium's high failure rate in many settings (Sarantidis and Waters, 1981; Gelenberg et al., 1989; Markar and Mander, 1989; O'Connell et al., 1991; Vestergaard, 1992; Okuma, 1993; Gitlin et al., 1995; Denicoff et al., 1994; 1997a,b). Instead of the 80% lithium response rate that was often cited a decade ago, lithium responsiveness appears to be under 50%, even when adjunctive antidepressant treatment is considered as part of the "lithium" regimen. Depressive breakthroughs are typically more problematic than manic breakthroughs during lithium treatment.

LITHIUM REFRACTORINESS

Lithium responsivity decreases remarkably in the illness pattern characterized by a depressive episode first, followed by a swing into a manic episode, and then a well interval (the D-M-I pattern). The D-M-I pattern response rates are approximately 30% or less, compared with 70% or more if the sequence is M-D-I (Faedda et al., 1991). This also suggests the reduced impact of lithium on the initial treatment of depression as opposed to mania, to the extent that the second phase is, in part, a compensatory overswing from an inadequately treated first phase.

In addition, the lithium response rate is reduced to approximately 30% with dysphoric mania (McElroy et al., 1992; Swann et al., 1997), which is characterized by coexisting depression, irritability, anxiety, agitation, and an uncomfortable sense of manic hyperactivity rather than euphoria. Dysphoric mania is also associated with hypercortisolemia (Swann et al., 1991) and has many depressive components mixed into the activated state, making lithium less adequate in dys-

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Received for publication 23 June 1997; Accepted 23 June 1997

phoric mania than in euphoric mania (Swann et al., 1997). Moreover, in the most recent study of lithium in long-term prophylaxis reported by Bowden (1996), lithium was surprisingly less effective in the prophylaxis of depression than placebo, while valproate was more effective than either lithium or placebo.

In a group of 66 lithium-refractory patients referred to the National Institutes of Mental Health (NIMH) for clinical investigation of their refractory bipolar illness, several subtypes of non-responsiveness were identified. Thirty-five percent of the patients were found to have had a pattern of initial responsivity to lithium, followed by a gradual loss of efficacy, consistent with pharmacodynamic tolerance (Post et al., 1993). A pattern consistent with discontinuation-induced refractoriness was observed in 13.8% of the patients (Post et al., 1992a, 1993). The rest of the patients, with few exceptions, appeared to be unresponsive to lithium from the outset.

It remains to be determined how these response rates compare with the rates for the general population not screened for initial refractoriness. However, in the recent study of Denicoff and associates (1997a,b), only one-third of the bipolar outpatients showed an initially good response to lithium after 1 year, even allowing for adjunctive antidepressants and neuroleptics as required. These outpatients were recruited from newspaper ads and not from our inpatient unit, and more than 75% were working, indicating they were not a particularly refractory subgroup of patients initially, and yet they had poor responsivity to lithium (as well as to carbamazepine monotherapy, as noted later).

In this outpatient population (Denicoff et al., 1997a,b), depression was a greater problem than mania, with patients having some degree of depression 33.7% of the time and some degree of mania 26.2% of the time in the year prior to the study, even with the best available treatment in the country. In the prospective treatment year on lithium, depression of moderate severity associated with a substantial sense of functional incapacity (moderate to marked on the Life Chart Methodology [LCM]) was evident 19.5% of the time, and mania 1.6% of the time in the two-thirds of the patients who were lithium nonresponders. This data further highlights the major problem of depressive breakthroughs on lithium, even when adjunctive antidepressant treatment as necessary is allowed.

CARBAMAZEPINE AS AN ADJUNCT AND ALTERNATIVE TREATMENT

While 19 double-blind studies of various designs suggest the acute antimanic efficacy of carbamazepine (Post et al., 1996), fewer controlled studies of carbamazepine in depression (Table 1) have been completed and the data are more equivocal. Table 2 summarizes studies of carbamazepine in prophylaxis, wherein carbamazepine was used in a randomized or blind or otherwise partially controlled design. These prophylactic studies suggest that carbamazepine may be effective in some 60% of patients, often in those who are refractory to lithium.

TABLE 1. Carbamazepine in acute depression[a]

Open studies			Controlled studies		
Investigator (s)*	Responders		Investigator (s)*	Responders	
Okuma et al. (1973, 1975)	3/9	BP	Wunderlich et al. (1983)	11/13	BP/UP
Folks et al. (1982)	3/4	2 BP 2 UP	Neumann et al. (1984)	5/5	BP
Barker and Eccleston (1984)	1/1	UP	Schaffer et al. (1985)	1/1	UP
Sethi and Tiwari (1984)	3/5	BP/UP	Post et al. (1986 and unpublished observations)	17/57	BP/UP
Arap Mengech (1985)	1/5	BP	Foster et al. (1989)	4/4	2d degree depression
Nurberg and Finkel (1985)	1/1	BP	Small (1989, unpublished observations as cited in Small, 1990)	9/28	BP/UP
Prasad (1985)	11/12	UP			
Stuppaeck et al. (1990)	20/24	6 BP 18 UP			
Cullen et al. (1991)	7/16	3 BP 13 UP			
Svestka et al. (1991)	24/37	UP			
Dilsaver et al. (1996)	17/27	BP			
Moderate to marked responders	91/141 (65%)				47/108 (44%)
All studies	138/249 (55%)				

[a]*BP = bipolar disorder; UP = unipolar disorder.*

TABLE 2. Controlled and partially controlled studies of carbamazepine (CBZ) and oxcarbazepine prophylaxis in affective illness[a]

Investigators (design)	Placebo	CBZ responders	% Response	Lithium responders	% Response
Ballenger and Post (1978)	(D-BL, M)	6/7	86	(—)	(—)
Post et al. (1983)					
Okuma et al. (1981)	(D-BI)	6/10	60	(—)	(—)
Svestka et al. (1985)	(R)	14/24	62	12/24	50
Kishimoto and Okuma (1986)	(C)	(?/18)	↓ # hospitalizations vs. Li	(—)	(—)
Cabrera et al. (1986)	(R)[b]	2/4	50	3/6	50
Placidi et al. (1986)	(D-BL, R)	21/29	72	20/27	74
Watkins et al. (1987)	(D-BL, R)	16/19	84	15/18	83
Elphick et al. (1988)	(D-BL, R)	3/8	37	8/11	73
Lusznat et al. (1988)	(D-BL, R)	?/9	↓ Fewer depressions	?/5	(—)
Bellaire et al. (1990)	(R)	34/40	85	42/49	86
DiCostanzo and Schifano (1991)	(R)[c]	(?/16)	Li+CBZ fewer episodes than Li alone	(?/16)	(—)
Mosolov (1991)	(R?)	?/30	Episodes ↓ 58%	?/30	Episodes ↓ 54%
Coxhead et al. (1992)	(D-BL, R)	7/15	47	7/16	44
Denicoff et al. (1997b)	(B, R)	11/35	31	14/42	33
All controlled and partially controlled studies		120/91	63	121/193	63
All open studies		390/629[d]	62		

[a] *Double-blind (D-Bl); blind (B); cross-over (C); mirror image (M); randomized (R); (—) not stated.*
[b] *Oxcarbazepine.*
[c] *Pseudo randomized to Li vs. CBZ and Li; greater antimanic and antidepressant efficacy in 1st year vs. Li alone.*
[d] *Includes carbamazepine combination therapies.*

In the study of Denicoff et al. (1997b) noted previously, neither lithium nor carbamazepine monotherapy was highly effective in this outpatient population; only 31.5% of the patients showed a moderate or marked response to carbamazepine on the modified Clinical Global Impressions (CGI) scale. This was partially attributable to carbamazepine's significantly reduced of efficacy against manic episodes compared with lithium, while there was a non-significant trend for carbamazepine's greater effectiveness in depression. However, when lithium and carbamazepine were used in combination, there was an overall 51.8% response rate, and a 53.3% response rate in those patients with a past history of rapid cycling. These data suggest the potential utility of carbamazepine in combination with lithium, as previously suggested by other acute studies (Kramlinger and Post, 1989a,b). In these studies, lithium appeared to be a useful adjunct to carbamazepine non- or inadequate responders, and a modicum of data exists in the reverse, wherein carbamazepine may be a useful adjunct to lithium non-responders (Kwamie et al., 1984).

In an acute study of carbamazepine administered blindly to unipolar and bipolar refractory patients, a 34% moderate-to-marked response rate was observed (Post et al., 1986) and this rate has continued as 30% (17 of 57 patients) showed moderate-to-marked response in our expanded series (Post et al., unpublished observations). Those patients with more severe and clearly episodic depressions were among those who responded better than those patients with fewer and more chronic depressions. Moreover, paradoxically, those with the greatest suppression of thyroid function were among those who had the best antidepressant response. This finding was initially observed by Joffe et al. (1984) and has remained as a correlative finding with the magnitude of the antidepressant effect correlating with the degree of decrease in free T_4 ($r = -0.56$, $P < 0.001$) (Post et al., 1997a). Recently, Dilsaver et al. (1994) reported a high response rate (17 of 27, 63%) to carbamazepine in bipolar refractory depression.

We began investigations of carbamazepine because of its unique ability to suppress amygdala-kindled seizures better than cortical-kindled seizures (Albright and Burnham, 1980), and because it otherwise was a highly effective anticonvulsant for seizures originating in mediotemporal structures (Bellenger and Post, 1978; Post and Uhde, 1985). However, there is currently little evidence that responsivity in bipolar affective illness is related to the "limbic" effects of the drug. One way we attempted to make this link was to assess the degree to which patients with affective illness had prominent psychosensory symptoms typically associated with complex partial seizures to the temporal lobe, such as déjà vu, olfactory illusions, etc. (Silberman et al., 1985). When patients had substantial numbers of these symptoms, even though they had primary affective illness and no evidence of a seizure disorder, these symptoms did not predict who would respond to carbamazepine in either acute depression or mania or, more recently, in long-term prophylaxis

(Ali et al., 1997). Thus these symptoms, to the extent that they are surrogate markers for limbic dysfunction, are not predictive of acute or long-term psychotropic responsivity to this anticonvulsant, although this has been suggested in uncontrolled studies by a variety of other investigators (Varney et al., 1993).

More recently, however, Ketter et al. (1996) have observed that patients with global hypermetabolism, including in the mediotemporal structures, were more likely to be carbamazepine responders than those with the more classical pattern of frontal or global hypometabolism. This is understandable from the view that carbamazepine, in general, appears to decrease cerebral glucose utilization, which may lead to a relative normalization of patients with hyperactivity at the outset. In contrast, those patients with the more typical pattern of frontal hypoactivity showed good response to the calcium channel blocker nimodipine (as discussed later). These data are among the first to suggest that evidence of limbic dysfunction at the level of increased metabolism could be associated with a higher response rate to carbamazepine (>50%) compared with those patients with relative hypometabolism (in which none showed good acute antidepressant response).

How these preliminary data of a potential relation of response to a basal pattern of hypermetabolism link to the biochemical effects of carbamazepine remains to be further examined (Post et al., 1992b, 1994, 1997c). However, it is apparent that carbamazepine is highly atypical in its biochemical profile compared with traditional antidepressants, even though it has a structure approximately resembling the tricyclic antidepressant (TCA) imipramine. In contrast to the TCAs, carbamazepine is a very weak reuptake blocker of norepinephrine, though not of sufficient potency to account for its psychotropic properties. Instead, it appears to decrease norepinephrine release and turnover, and also has opposite effects on beta-receptor regulation compared with most antidepressant agents, which downregulate cortical beta-receptors. Similarly, while most antidepressants decrease cortisol secretion (via upregulating glucocorticoid receptors), carbamazepine appears to do the opposite (Post et al., 1992b, 1994, 1997c). Even in normal volunteers, carbamazepine increases escape from dexamethasone suppression and urinary free cortisol (Rubinow et al., 1984; Perini et al., 1992).

In addition, carbamazepine is effective at peripheral-type benzodiazepine receptors characterized by binding of Ro5-4864 or PK-1195, which are involved in the control of neurosteroid biosynthesis and are quite dissimilar from the effects of central benzodiazepine ligands. In contrast, central benzodiazepine ligands, such as clonazepam, are active at the gamma aminobutyric $(GABA)_A$-benzodiazepine receptor-chloride ionophore complex and increase chloride influx. Carbamazepine also decreases cerebrospinal fluid (CSF) somatostatin and neuropeptide Y (NPY), the latter of which could be associated with carbamazepine's prominent anti-anxiety effects in both affectively ill patients and in those patients with epilepsy (Post et al., 1992b, 1994, 1997c). Thus, there are a variety of highly atypical biochemical effects of carbamazepine that could account for its potential use either alone or as an adjunct in patients with refractory affective illness, particularly in those who have had adequate trials with more traditional antidepressant and mood stabilizing modalities.

VALPROATE

Valproate (and its enteric-coded congener divalproex sodium [Depakote®]) has recently been approved for first-line treatment of acute mania. In addition, it is now widely used in long-term prophylaxis and appears to have a range of effects in preventing manic and depressive recurrences, as noted in a series of open studies (Emrich et al., 1984; Lambert, 1984; McElroy et al., 1988; Calabrese et al., 1992, 1994; Schaff et al., 1993; Lambert and Venaud, 1995; Post et al., unpublished observations). As noted previously, Bowden (1996) reported divalproex sodium more effective than lithium or placebo in the prevention of bipolar depression. However, in the studies of Calabrese et al. (1992, 1994) a much lower efficacy rate of valproate was evident in acute depression (compared with acute mania), with more equivalent efficacy in the prophylaxis of depressive compared with manic episodes.

The overall acute antidepressant efficacy of valproate, as well as its spectrum of prophylaxis and utility in refractory depression, remains to be further examined, as do other potential clinical and biological correlates of valproate response. Uncontrolled data (Calabrese et al., 1993, 1994) suggest that better antidepressant responders to valproate include those patients with non-psychotic mania, a pattern of prior stable or decreasing cycle frequencies in rapid cyclers, and absence of comorbid personality disorder.

Valproate has a spectrum of effects that might, additionally, make it useful in a variety of co-morbid conditions in refractory bipolar depression. In particular, a number of double-blind, placebo-controlled studies document the utility of valproate in the prevention of migraine (Balfour and Bryson, 1994), a syndrome that is highly comorbid with bipolar illness. Additionally, valproate has been reported to have excellent anti-anxiety and anti-panic effects, at least in a subgroup of patients (Keck et al., 1993). These data are convergent with valproate's particular utility in patients with dysphoric and anxious mania, in whom, in contrast to lithium, there is no reduction in responsivity (Bowden et al., 1994). In addition, valproate is highly effective in many rapid cycling patients (Calabrese et al., 1992, 1993), in contrast to lithium, which appears selectively less effective in rapid cyclers. The mechanisms of action of valproate that underlie a broad spectrum of clinical anticonvulsant and psychotropic

effects are thought to involve its GABAergic mechanisms (Post et al., 1994), but this remains to be directly tested and clarified.

DIHYDROPYRIDINE L-TYPE CALCIUM CHANNEL BLOCKERS (CCBS)

While a number of controlled studies suggest the antimanic utility of verapamil (Dubovsky, 1995) (Table 3), the randomized acute depression study of Hoschl and Kozeny (1989) indicates that verapamil is no more effective than placebo and less effective than routine antidepressant treatment. These data led to our search for a more effective calcium channel blocker that might have a spectrum of antidepressant and prophylactic effects exceeding those of verapamil. Thus, we chose to study the dihydropyridine L-type CCB nimodipine because of its: (1) ability to penetrate the central nervous system (CNS); (2) failure to show as robust a tolerance phenomena in the treatment of migraine (as do many other CCBs); (3) better profile in many types of animal seizure models compared with verapamil; and (4) greater ability to block cocaine hyperactivity

TABLE 3. Calcium channel blockers in affective illness[a]

Open studies	Responders	Blind studies	Responders
Verapamil (phenylalkylamine)		Verapamil (phenylalkylamine)	
Gitlin and Weiss (1984)	1/1 BP	Dubovsky et al. (1982)	1/1 M
Brotman et al. (1986)	6/6 M	Dubovsky and Franks (1983)	2/2 M
Solomon and Williamson (1986)	2/2 M	Giannini et al. (1984)	10 M equal to lithium, better than placebo
Walton et al. (1996)	?M		
Barton and Gitlin (1987)	0/8 M (acute)	Giannini et al. (1987)	20 M equal to lithium
	1/4 M (prophyl)	Giannini et al. (1989)	10 M equal to lithium, better than valproate
	2/2 M[b]		
Patterson (1987)	1/1 M	Dubovsky et al. (1985)	1/1 M[b]
Pollack and Rosenbaum (1987)	1/1 UP	Dose et al. (1986)	7/8 M
Deicken (1990)	1/1 BP	Dubovsky et al. (1986)	5/7 M vs. 1/7 Li
Hoschl et al. (1990)	4 BP-Dep/7 UP, verapamil more effective than antidepressants and neuroleptics	Dubovsky and Franks (1987)	1/2 M Using Li-Verapamil combination
		Hoschl and Kozeny (1989)	12 M significantly improved over neuroleptics, neuro. + Li
		Garza-Trevino (1990)	17 M equal to Li
		Garza-Trevino et al. (1992)	12 M equal to Li
		Hoschl (1983)	1/1 Dep.
		Janicak et al. (1994)	3/10 vs. 1/11 Li
Nimodipine (dihydropyridine)		Nimodipine (dihydropyridine)	
Brunet et al. (1990)	6/6 M	Pazzaglia et al. (1993)	7/23 BP[d]
Manna (1991)[c]	12 M	Pazzaglia (unpublished observations)	0/4 UP[d]
		McDermut et al. (1995)	3/3 RBD[d]
		Eckmann (1985a)(2)	27/30 Dep.
			29/30 Dep.
		Montenegro et al. (1985)	22/37 (59%) able to discharge with amitriptyline or nimodipine vs.
Goodnick (1995)	2/2 BP		1/38 (2.5%) able to discharge on placebo
Grunze et al. (1996)	1/1 BP (Li+Nimod)		
Walden et al. (1994)	6/7 Dep.		
Flunarizine (dihydropyridine)			
Lindelius and Nilsson (1992)	1/1 M		
Diltiazem (benzothiazepine)		Flunarizine (dihydropyridine)	
Caillard (1985)	5/5 M	Eckmann (1985b)	14/17 Dep.
Nifedipine (dihydropyridine)		Isradipine (dihydropyridine)	
Eccleston and Cole (1990)	0/1 UP	McDermut et al. (1995)	2/2 BP nimodipine responders
		Pazzaglia et al. (unpublished observations)	
Moderate to marked responders	35/48 (73%)		123/172 (72%)

[a] *BP = bipolar disorder; M = mania; Dep. = depression; UP = unipolar; RBD = recurrent brief depression.*
[b] *Drug-induced hypomania.*
[c] *Lithium and nimodipine combination in prophylaxis better than either drug alone.*
[d] *Combined results from three studies listed.*

and dopamine overflow (Pazzaglia et al., 1993, unpublished observations; and see Post et al., 1997b).

As initially reported (Pazzaglia et al., 1993), we observed that 5 of the first 12 evaluable patients had a clinically relevant, robust response to nimodipine, including patients with recurrent brief depression, and rapid and ultradian cycling frequencies. Responsitivity was confirmed and re-confirmed in some of these patients in a B-A-B-A design (McDermut et al., 1995). This response rate has continued to be observed in a slightly larger series, with responsivity in 10 of the first 30 patients studied with nimodipine monotherapy (Pazzaglia et al., unpublished observations), although almost all of these patients needed their regimens further supplemented with another agent, such as carbamazepine.

Carbamazepine augmentation of nimodipine, however, was effective (moderate or marked response on the CGI) in only five of 14 patients treated with the combination. Of considerable interest were several patients who were clear nimodipine responders to either monotherapy or combination therapy and transitioned on a double-blind basis to maximally tolerated doses of verapamil, without maintaining response. They later either re-responded to nimodipine or to another dihydropyridine L-type CCB such as isradapine, further confirming not only the initial responsivity to this drug class, but also suggesting that responsivity might be better conferred by the dihydropyridine subtype of L-type CCBs (with its binding site deep inside the calcium channel) rather than the phenylalkylamine verapamil (which has different channel characteristics).

While there is some evidence that patients with extreme rapidity of cycling fluctuations occurring within a 24-h period (ultra-ultra rapid or ultradian cycling) are among those who respond best to the dihydropyridines, the question of whether this subgroup is a selected target remains to be further delineated (Pazzaglia et al., 1993). Moreover, as noted previously, patients with the more classical pattern of global and frontal hypometabolism were among those who responded best to nimodipine (Ketter et al., 1996). Much work remains to be done in order to better delineate the precise role of the CCBs in the treatment sequence of bipolar refractory depression (see Table 3).

LAMOTRIGINE (LAMICTAL®)

A preliminary report (Calabrese, 1996) suggested that lamotrigine, the newly approved anticonvulsant for add-on therapy, might have excellent antidepressant and, potentially, mood-stabilizing properties. Sixty-seven patients were studied in an open fashion, usually with the drug as an add-on to other previously ineffective treatment regimens; 27/39 (69%) patients who presented in the depressed phase and 19/25 (76%) in the manic phase showed moderate to marked improvement.

We have also seen a good response in 8 of the first 18 patients (59%) randomized to blind lamotrigine monotherapy compared with gabapentin or placebo (Frye et al., 1997b). Several patients with refractory depression profiles were among those who showed a good response. Clearly, much work is required in order to delineate the utility of this agent in refractory depression, although the preliminary observations in a limited open study and a blind study are promising.

Lamotrigine should be initiated slowly in monotherapy with one 25-mg pill for the first 2 weeks and then 50 mg for 2 weeks, with slow increases thereafter in order to avoid a moderately high incidence of rash. The rate of increase should be cut in half if patients are on a regimen including valproate, which can markedly increase lamotrigine blood levels, the propensity for rash, and more serious dermatologic complications.

The precise anticonvulsant or psychotropic mechanisms of action of lamotrigine remain to be delineated (Fitton and Goa, 1995; Messenheimer, 1995). However, it is of considerable interest that lamotrigine, like valproate, is a broad spectrum anticonvulsant, effective not only in complex partial and generalized seizures, but also in absence and atonic seizures, in contrast to carbamazepine, which can exacerbate absence seizures. This is of considerable importance as recent studies have suggested that carbamazepine and lamotrigine, as well as phenytoin, have highly similar properties in the blockade of type 2 sodium channels and consequent release of excitatory amino acids such as aspartate and glutamate (Lang et al., 1993; Davies, 1995). However, the differential clinical profile of these drugs in epilepsy (Brodie et al., 1995) and the preliminary data that lamotrigine may be effective in some patients who are inadequate responders to carbamazepine (Calabrese, 1996; Frye et al., 1997b) suggest that additional mechanisms not shared by carbamazepine will eventually be uncovered for lamotrigine.

GABAPENTIN (NEURONTIN®)

This newly approved anticonvulsant for adjunctive therapy may also have some mood-stabilizing effects (Dimond et al., 1996; Frye et al., 1997b; McElroy et al. 1988, Suppes et al. 1992, Young et al., 1997). Its overall efficacy in depression does not appear to be as robust as in mania in initial open observations. In the first 18 patients studied in a 6-week blind monotherapy phase in our population of refractory patients (Frye et al., 1997b). Seven of the 39% of the patients in our population did show clinically relevant responses to gabapentin, including positive effects on mood sleep and anxiety. Whether its prominent effects on the L-amino acid transport mechanism and resulting increases in brain GABA levels are related to its anticonvulsant and psychotropic properties remains to be further delineated (Beydoun et al., 1995; Ketter et al., 1997).

RATIONALES FOR COMBINATION THERAPY

In light of the evidence that traditional unimodal antidepressants can precipitate mania in approximately one-third of bipolar patients (Rouillon et al., 1992; Altshuler et al., 1995; Denicoff et al., unpublished observations) and cause cycle acceleration in about one-fifth of bipolar patients (Wehr and Goodwin, 1979), there appears to be some rationale for using several mood stabilizers in combination prior to the use of an antidepressant. It should be acknowledged from the outset that the data upon which this clinical formulation or algorithm is based are highly preliminary and provisional.

Three or four indirect bits of data are pertinent and the proposition remains to be systematically tested with the comparison of a mood stabilizer to an antidepressant in prospective randomized trials; (1) there is evidence the utility of using several mood stabilizers in combination; (2) the recognized potential liabilities of the unimodal antidepressants in bipolar patients a second rationale; and are a third piece of data involves our refractory bipolar patients admitted to the NIMH over the past 25 years, wherein the vast minority (i.e., only about 15%) have been discharged on a regimen including an antidepressant.

(1) MOOD STABILIZERS IN COMBINATION

We have already alluded to the data on the clinical efficacy of various combinations of mood stabilizers in otherwise refractory bipolar illness, i.e., lithium and carbamazepine (Kramlinger and Post, 1989a,b; Okuma, 1993; Denicoff et al., unpublished observations); lithium and valproate (Emrich et al., 1985; McElroy et al., 1988; Calabrese and Delucchi, 1990; Sharma et al., 1993); and nimodipine and carbamazepine (Pazzaglia et al., 1993, unpublished observations). In addition, an open case series (Keck et al., 1992) and a blind case study (Ketter et al., 1992) suggest that as in refractory epilepsy, the combination of carbamazepine and valproate, two agents with putatively different mechanisms of action, may be associated with a good clinical response in the absence of a good response to either monotherapy. The finding that lamotrigine, alone or in combination with previously ineffective treatments (often involving mood stabilizers), has such a high percentage of response in refractory depression (Calabrese, 1996), is also supportive of the potential utility of several mood stabilizers in combination for the treatment of refractory bipolar depression.

(2) UNIMODAL ANTIDEPRESSANT LIABILITIES

Although the issue of tricyclic induction of mania and cycle acceleration is controversial, the data of Wehr and Goodwin (1979) and Altshuler et al. (1995) provide clear evidence that some patients with initial rapid cycling presentations cycle even faster on antidepressants, and then cycle more slowly upon antidepressant discontinuation. Assuming this potential liability occurs in approximately 25% of patients (Altshuler et al., 1995), and given that predicting which bipolar patients will show this phenomenon is currently impossible, the rationale for considering the addition of a second mood stabilizer prior to the addition of an antidepressant, particularly in patients with more cyclic presentations, appears to have some merit.

(3) NIMH RETROSPECTIVE DATA

The data of Frye (1996) also support the notion that many depressed patients with refractory illness can be treated with a variety of approaches not typically involving antidepressant modalities. Frye analyzed the discharge medications of patients over successive 5-year epochs in the tertiary referral-clinical research unit of the Biological Psychiatry Branch, NIMH, and found that the Branch was able to maintain approximately the same or greater percentage of patients discharged with marked or moderate improvement on the CGI (75% or more) within each 5-year epoch in the past 25 years. However, while patients were able to be discharged on monotherapy more than 75% of the time in 1970–1974, this decreased to less than 25% of the time in the most recent 5-year period, and the average number of medications increased to 3.3 per patient. Yet, we only had to use antidepressants in approximately 15% of the patients. These data, while retrospective and not based on a randomized approach to antidepressants, nonetheless reveal that the substantial majority of patients with refractory presentations can be managed largely in the absence of the unimodal antidepressants.

UNIMODAL ANTIDEPRESSANTS IN REFRACTORY BIPOLAR DEPRESSION

When using the unimodal antidepressants, the current preference of most experts in bipolar illness is to first use bupropion. This preference is based on the modicum of data that bupropion may have mood-stabilizing properties on its own (Shopsin, 1983; Wright et al., 1985), that it is useful in conjunction with lithium carbonate in rapid-cycling patients (Haykal and Akiskal, 1990), and that it may have a lesser liability for switching induction than many other antidepressant modalities. For example, Sachs et al. (1994) conducted one of the few controlled studies comparing the liabilities of two different antidepressants for switch induction, and found equal acute antidepressant efficacy of bupropion, with its dopaminergic effects, and desipramine, with its largely selective noradrenergic effects. However, the subsequent switch rate into mania was greater in those patients randomized to desipramine compared with bupropion.

In informal polling of experts at Continuing Medical Education (CME) and other conferences on bipolar illness, there also appears to be a preference for first use of bupropion over the selective serotonin reuptake inhibitors (SSRIs), although this remains to be directly assessed. Bupropion also has the potential asset of not causing sexual dysfunction at the same rate as the SSRIs, and is one of the few antidepressants associated with an average weight loss rather than weight gain. Both of these attributes can be particularly important for patients with bipolar illness, who are often on mood stabilizers associated with weight gain (i.e., especially lithium and valproate). Moreover, Barrickman et al. (1995) reported that bupropion was as effective as methylphenidate in the treatment of attention-deficit hyperactivity disorder (ADHD), raising the possibility that bupropion could be used when there is a positive family history of bipolar illness and potential confusion between ADHD and childhood-onset bipolar illness.

The initial data of Zis et al. (1979) suggested that the rapidity of onset to the switch process was related to noradrenergic mechanisms as assessed by urinary 3-methoxy-4-hydroxyphenylethylene glycol (MHPG). Thus, to the extent that the SSRI venlafaxine has added antidepressant potency in refractory depression and is potent on both noradrenergic and serotonergic reuptake mechanisms, it would be of considerable importance to see whether it shares the liability of a tricyclic antidepressant (such as desipramine) for a greater switch rate or cycle induction.

There may be some merit in adding venlafaxine to bupropion in refractory bipolar patients in order to enhance reuptake blockade of all three neurotransmitter systems (norepinephrine and serotonin with venlafaxine, and dopamine with bupropion). While bupropion is a relatively weak blocker of dopamine reuptake, it appears to sufficiently increase dopamine levels acutely and chronically in the striatum and nucleus accumbens in experimental animals at clinically relevant doses (Nomikos et al., 1989). In this manner, one could conceptualize the hypothetical creation of a relatively "broad spectrum" antidepressant regimen with enhancement of all three amine systems with the venlafaxine-bupropion combination, perhaps bearing some similarity to the broad spectrum effects of the monoamine oxidase inhibitors (MAOIs), which enhance all three neurotransmitter systems at the level of MAO inhibition and prevention of amine breakdown. This could be of some potential importance, in light of the evidence (Himmelhoch et al., 1991) that there is a much better rate of antidepressant response in bipolar depression (81%) to tranylcypromine compared with a traditional tricyclic, imipramine (48%). Whether this higher response rate in bipolar patients to tranylcypromine would be shared by any of the newer amine selective antidepressants remains to be determined by further systematic randomized studies.

The buopropion-venlafaxine combination or other incompletely effective antidepressant regimen could then be further augmented with T_3 potentiation (25–37.5 μg of T_3 [cytomel]) in the AM, assuming that the patient was already on lithium (see Joffe and Singer, 1990). If the patient was not already on a regimen including lithium, it might be advisable to potentiate with lithium HS 750–900 mg in an attempt to achieve blood levels in the 0.7 to 0.8 meq/l range where there is some evidence (at least from unipolar depression) that this may be a threshold blood level for augmentation with lithium. Thus, patients who do not tolerate full doses of lithium for prophylaxis may, nonetheless, tolerate lower doses in this attempted acute augmentation strategy.

If this approach is not effective based on a combination of antidepressants with potentiation strategies, one may then be in a position to discontinue the venlafaxine (because of its serotonergic reuptake properties) under the cover of bupropion (and other augmentation strategies) on the way to consideration of an MAOI such as tranylcypromine. This strategy may also have the advantage of avoiding or interrupting the repeated use of different but similarly acting SSRIs, on the assumption that little advantage would be gained because of their similar mechanisms of action.

In addition, until direct evidence is available that nefazadone has additional efficacy in bipolar depression greater than that achieved by the SSRIs, one might more expeditiously move through the treatment algorithm, first with venlafaxine augmentation and then earlier use of an MAOI following the discontinuation of agents that are potent at the serotonin reuptake site. This strategy may avoid a long series of sequential trials with different serotonin-active antidepressants should the data ultimately demonstrate a rather low response rate to different agents in this class in the face of non-response to a single SSRI.

THYROID AUGMENTATION, REPLACEMENT, AND HYPERMETABOLIC STRATEGIES

As noted previously, T_3 potentiation appears to have considerable merit in the treatment of unipolar refractory depression, and data from our laboratory suggest that one-third of patients with either unipolar or bipolar refractory depression may respond to either of these augmentation strategies (Frye et al., 1997a). There was a trend in our data for women (44%) to be more responsive to T_3 than men (10%), as has previously been suggested in the literature. The use of physiological replacement doses of T_4 (75–100 μg/day) with their TSH suppressant effects may also be of clinical utility in bipolar depression, as 43.5% responded in our data (53.3% in women and 25% in men).

In addition, recent data (Bauer and Whybrow, 1990) indicate that high-dose T_4 treatment (150–400 μg/day targeted towards achieving a free thyroxin index 150% of normal) may be particularly helpful as an

adjunctive treatment in rapid cycling patients. The report of Baumgartner et al. (1994) further suggests that this high-dose T_4 augmentation strategy may be useful in patients with persistent refractory depression as well. The data of Bauer and Whybrow (1990), indicating improvement in both manic and depressive phases with T_4 augmenting strategies, speaks to the potential importance of this modality for bipolar illness. However, systematic long-term trials remain to be conducted, and the issue of whether some patients lose responsivity to such thyroid augmentation strategies with the development of tolerance also requires further exploration.

FURTHER AUGMENTATION STRATEGIES

PSYCHOMOTOR STIMULANTS

The role of psychomotor stimulants as acute augmentation has not been systematically explored, although it is apparently widely used by some experts in the field (J. Fawcett, personal communication). However, Fawcett has indicated that this is not a useful long-term strategy as many patients appear to develop tolerance to this modality, and therefore this strategy should perhaps be reserved for temporary augmentation while awaiting more effective antidepressant response to other modalities.

Fawcett has also observed that tolerance does not appear to develop when the psychomotor stimulants are combined with MAOIs. This strategy should, perhaps, be reserved for the end of the treatment algorithm in only the most refractory patients, as the *Physicians' Desk Reference* (PDR) lists an absolute contraindication for combining stimulants and MAOIs. Nonetheless, this strategy appears to be tolerated in most patients (Feighner et al., 1985; Fawcett et al., 1993).

LIGHT IN AM AND MELATONIN HS

Systematic trials of augmentation with bright light (greater than 7,500 lux) may be worth considering in patients with marked disruption of circadian rhythmicity and the typical bipolar hypersomnia (Yamada et al., 1995). In these instances, high intensity light might be most useful in the A.M., although this entire issue needs to be revisited with more systematic prospective randomized studies.

An additional approach to altered sleep-activity cycles (which are common in bipolar patients) might be to use melatonin adjunctively at night, although this, too, requires caution and prospective studies. In addition, we have heard isolated reports of exacerbation of sleep or mood in some patients when using melatonin supplementation.

INOSITOL

Inositol (12–14 g/day) has recently been reported to have antidepressant and antianxiety effects (Benjamin et al., 1995). This remains to be more systematically explored in bipolar patients (in light of no reports of patients switching) and in those patients who are already being treated with lithium. Theoretically, inositol should not only relieve some lithium-induced side effects, but could potentially reverse its therapeutic efficacy to the extent that reduced phosphoinositide (PI) turnover on lithium is related to its mechanism of action and the associated depletion of inositol is a reflection of this blockade. One would then predict that inositol augmentation might make carbamazepine even more effective, since carbamazepine has the opposite effects of lithium on the inositol phosphatase system: lithium blocks this enzyme and carbamazepine enhances the function of this enzyme (Vadnal and Parthasarathy, 1995). We are not yet aware of any clinical data exploring this possibility, however.

CHOLINE

Stoll et al. (1996) have reported that potentiation with choline may be helpful in stabilizing mood in refractory cycles, and this approach, too, requires further systematic study.

FOLATE AND ASCORBATE

The vitamins folate and ascorbate have each been reported to have some beneficial effects on amelioration of mood in long-term prophylaxis of bipolar patients and, in light of their benign side-effects profile, might be worthy of consideration in the treatment regimen of the refractory bipolar patient (Naylor and Smith, 1981; Kay et al., 1984; Coppen et al., 1986).

APPROACHES TO DOPAMINE IN REFRACTORY DEPRESSION: ANTAGONISTS AND AGONISTS

Some patients appear to require neuroleptics for long-term mood stabilization, including recurrent depressive episodes, in the uncontrolled observations of Hendrick et al. (1994). However, other investigators have reported that neuroleptics can exacerbate the depressive phases of bipolar illness, increasing the frequency and/or duration of depression (Kukopulos et al., 1980; Ahlfors et al., 1981). These potential liabilities and the availability of newer atypical neuroleptic agents should make one increasingly use these atypical drugs with their lesser liability for tardive dyskinesia. This is particularly the case as bipolar patients appear to be at equal or greater risk than schizophrenic patients for developing tardive dyskinesia (Waddington and Youssef, 1988; Sernyak and Woods, 1993) and the intermittent use of neuroleptics is not a protection against this liability (Jeste and Wyatt, 1982). Recent reviews indicate a rather substantial incidence of tardive dyskinesia ranging from 20–40% in large samples of bipolar patients exposed to typical neuroleptics followed prospectively (Hunt and Silverstone, 1991).

Thus, the utility of low doses of risperidone require further exploration, although McEvoy et al. (1993) have found that some patients may have an increased liability for switching into mania when treated with this agent. Clozapine appears to have a particularly good spectrum of efficacy in refractory bipolar illness characterized by either dysphoric mania or rapid cycling (Suppes et al., 1992; Calabrese et al., 1996; Frye et al., 1996). However, it has the considerable liability of inconvenience, cost, and risk of agranulocytosis, requiring weekly blood monitoring. The new atypical agent olanzapine has a profile most similar to clozapine and it remains to be investigated whether this newly approved agent will assume a similar role in the treatment of refractory bipolar patients (Tamminga and Lahti, 1996).

A potentially unique approach to the dopamine system could be attained with the tricyclic antidepressant trimipramine (Surmontil®). This approved agent had an unknown mechanism of action since it was not a potent reuptake blocker. More recently, it has been shown to be a moderately potent antagonist of D_2 and D_4 receptors with a profile somewhat similar to that of clozapine (Eikmeier et al., 1991; Gross et al., 1991). It has also been reported in open studies to be effective in the treatment of acute schizophrenic episodes. Therefore, in light of its D_2 and D_4 blocking properties, as well as its efficacy as an antidepressant, Eikmeier and associates (1991) have recommended using trimipramine as a treatment trial in some refractory bipolar patients.

The role of the direct dopamine agonists such as bromocriptine (Colonna et al., 1979) clearly requires further exploration, and recent studies (Silverstone, 1984) suggest a potentially greater antidepressant efficacy of this agent in bipolar compared with unipolar depression. Bupropion's dopaminergic actions have been noted previously.

ROLE OF ELECTROCONVULSANT THERAPY (ECT)

Although ECT is effective in the treatment of both acute manic and acute depressive episodes, the issue of the appropriate regimen for long-term prophylaxis in prior pharmacological nonresponders is still open. After successful ECT intervention, one should consider the use of a novel prophylactic regimen rather than a return to the previously ineffective strategies in light of the data (Sackeim et al., 1990) in unipolar depression. Sackeim et al. (1990) found that these previously ineffective strategies remain ineffective after ECT. The issue of continuation treatment with ECT as a long-term prophylactic agent has received some study in isolated reports in the literature, but remains to be documented in even semi-systematic clinical trials.

In the face of the development of tolerance (i.e., the experience of breakthrough episodes to a previously effective pharmacological treatment), there would be many reasons to recommend ECT. In these instances, not only would one have a period of time off the original medication that could potentially lead to renewed responsivity (Weiss et al., 1995), but also one would have the asset of a very potent alternative treatment with ECT available during this medication-free interval. Thus, one might consider an acute intervention with ECT or a drug with a novel mechanism of action in the face of tolerance development, with the possibility of returning to the original treatment.

SUMMARY AND CONCLUSION

Thus, there appears to be a large variety of approaches to refractory bipolar depression. In contrast to several decades ago, wherein augmentation of lithium with antidepressants and neuroleptics was essentially the only treatment mode available, a panoply of treatment options now exist. However, their relative efficacy in different illness subtypes and stages remains to be better delineated, as do their optimal sequencing and use in combination in individual patients. It is the opinion of these authors and many of our colleagues in the field that initial use of several mood stabilizer drugs in combination may have a preferable long-term outcome in some rapid cycling patients, compared with the immediate use of a unimodal antidepressant with an inadequate single mood stabilizer, although this remains to be systematically studied. The use of thyroid augmentation strategies would appear to have merit in relationship to not only the potential treatment of lithium-related hypothyroidism, but also in augmenting antimanic and antidepressant effects.

As one moves toward some of the complex combination treatment strategies discussed in this chapter, one has to be particularly careful about drug interactions and their potential for toxicity as well as therapeutic effects. Perhaps a prevailing guideline would be to use these agents more carefully in combination therapy than in monotherapy, with slow upward titration of dose to individual patients' side effects thresholds, even in preference to targeting of conventional blood level windows. In this way, side effects can be avoided during the assessment of complex combination regimens.

In addition, one should be aware of potential pharmacokinetic interactions. For example, with the addition of valproate to carbamazepine, one should reduce the dose of carbamazepine, as valproate will not only increase the free fraction of carbamazepine based on displacement of protein binding, but will lead to increased accumulation of carbamazepine-10,11-epoxide. This epoxide is not measured in conventional assays but could contribute to the side effects profile (Ketter and Post, 1994). Similarly, valproate will markedly increase blood levels of lamotrigine; the starting dose of this agent should be substantially lower than conventional dosage when these two drugs are used in combination.

We suggest the utility of detailed mapping with a formal system—such as the Life Chart Methodology (LCM) (Leverich and Post, 1996)—of mood fluctuation vs. medications in order to optimize and rationalize complex combination therapy. In this way, not only can the nuances of partial response be better defined, but also basic decisions about the therapeutic index and relative likelihood of response can be more readily assessed. We have discussed the other merits of the life chart method as an important clinical treatment tool as well as a research tool in other venues, but reemphasize its potential great importance in the treatment of refractory cyclic bipolar patients, in whom an initial period of remission of depression may, in many instances, be as likely attributable to the natural course of illness as the current intervention being offered. As such, it behooves the clinician to have a systematic database for the more subtle issues of dose titration and sequential addition of medications in complex combination regimens.

In the face of inefficiency to one combination strategy, how one moves to the next strategy remains a highly individualized, clinically-based algorithm. We suggest the potential utility of moving towards a new set of mood stabilizers and then repeating some of the unimodal antidepressant additions and augmentation trials in an attempt to overcome refractory depression. Refractory depression in bipolar patients should be viewed as a medical emergency in light of the high potential for suicide in the illness in general (Chen and Dilsaver, 1996) and in patients who have either sustained or episodic refractory depressive breakthroughs.

In this regard, it should be noted that refractory depressed patients with highly cyclic presentations of their illness often do not feel that their brief "well" or hypomanic intervals are of benefit in enhancing a more optimistic view towards therapeutics. In fact, many patients report that cycling is more disruptive to their lives and, in some instances, they would prefer continuous depression to the episodic and unpredictable chaotic mood fluctuations that often accompany refractory bipolar illness. Thus, one should be particularly alert toward the potential for suicide in these patients and maintain a balance of hopeful optimism with careful suicide assessment in the pursuit of more optimal, even if complex, treatment algorithms.

As in other late phase medical syndromes and medical emergencies, complex combination treatment is often required. While it may at first consideration seem inappropriate to consider a regimen with four or five drugs for the treatment of refractory bipolar illness, this has been elevated to standard and routine practice in many other areas of medicine, such as the treatment of malignancies, tuberculosis, or congestive heart failure. In these instances, multiple therapeutic modalities with different mechanisms of action are often combined for optimal therapeutics.

With the availability of a variety of agents for bipolar illness, it now befits the field to engage in a series of novel and systematic clinical trials in order to better delineate the optimal design strategies for achieving the most rapid response rates in the highest numbers of patients, so that even the most refractory bipolar patients have an excellent chance at achieving substantial clinical remission.

Acknowledgement. Support of the Ted and Vada Stanley Foundation is gratefully acknowledged.

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